Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 7 and 24-67 are active in the application, with claims 24, 36, 47, and 57 being the independent claims. Claims 1-6 and 8-23 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 24-67 have been added. Support for claims 24-67 can be found in the claims as filed and throughout the specification. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Should the rejections not be withdrawn, Applicants respectfully request that a personal interview be scheduled with the undersigned and representative counsel from the assignee, Human Genome Sciences, Inc., prior to any subsequent Office communication.

Comments on the Restriction Requirement

In response to the Restriction Requirement dated June 28, 2002 (Paper No. 6), Applicants filed a complete reply on July 28, 2002, electing, with traverse, the invention of Group I consisting of claims *1-13 and 18* (*see*, Paper No. 6, page 2). In the same reply, Applicants also requested withdrawal of the sequence election requirement.

At page 3, lines 2-7, of the present Office Action (Paper No. 8), however, the Examiner states:

> Furthermore, the fragments in claim 7 are different proteins and are structurally distinct compounds and are unrelated to one another. The nucleotide sequences encoding them are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. § 121. Applicants may petition pursuant to 37 C.F.R. § 1.181 for examination of additional nucleotide sequences by providing evidence that the different nucleotide sequences do not cover independent and distinct inventions. The requirement is still deemed proper and is therefore made FINAL.

Thus, although Applicants' specific election was to the invention of Group I (consisting of claims 1-13 and 18, as set forth in Paper No. 6), the Examiner has now removed claim 7 from it's former inclusion in Group I, without issuing a subsequent Restriction Requirement (oral or written), and thus, providing Applicants with their right to traverse. Rather, in Paper No. 8, the Examiner has withdrawn claim 7 (as well as claims 14-17 and 19-23) from further consideration "pursuant to 37 C.F.R. § 1.142(b), as being drawn to a nonelected invention." Paper No. 8, page 3, line 10-12. Applicants respectfully traverse this action, as claim 7 was not "nonelected." Applicants respectfully request that the Examiner clarify the status of claim 7, which is still pending in the present case.

Concerning Applicants' request to withdraw the sequence election requirement, Applicants appreciate the Examiner's indication that polynucleotides encoding full-length, full-length minus the N-terminal methionine, mature, and 50 mer polypeptides have been rejoined. Paper No. 8, page 2, lines 6-8.

Objections Regarding Sequence Listing Requirements

At page 3 of Paper No. 8, the Examiner states that the Applicants are not fully in compliance with the sequence rules because the specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. Specifically, the Examiner mentions that Figure 2 is missing a SEQ ID NO: for CTGF-3, and that the specification should be reviewed for other missing sequence identifiers. Also, the Examiner states that the Applicants may bring the figure into compliance by amending either the Figure itself or the "Brief Description of the Drawings" section of the specification.

Applicants have reviewed the specification as requested by the Examiner and have made the necessary amendments. This objection has been overcome and should be withdrawn.

Consideration of Documents AS13 and AT13 from the IDS of May 31, 2002

At page 4 of Paper No. 8, the Examiner indicates that documents AS13 and AT13 have not been considered because "the relevance of the sequences disclosed in the references to the present sequences is impossible to ascertain in the absence of an alignment."

In response, Applicants respectfully assert that the references were properly cited in accordance with 37 C.F.R. §§ 1.97 and 1.98. "Once the minimum requirements of 37 C.F.R. 1.97 and 37 C.F.R. 1.98 are met, *the examiner has an obligation to consider the information.*" M.P.E.P. § 609 at 600-118 (Eighth edition, August 2001)(emphasis added). Applicants are unaware of an exception or special requirement for an alignment that applies

to references containing sequence information, and the Examiner has not identified any authority for such an exception or requirement. Indeed, the only references for which any explanation of relevance is required are those containing "information that is not in the English language." *Id.* at 600-122.

Accordingly, Applicants respectfully request that the Examiner consider the previously submitted references AS13 and AT13, and return an initialed copy of the Form PTO-1449 to Applicants with the next Office Action. For the Examiner's convenience, a clean copy of the relevant page of Form PTO-1449 filed May 31, 2002 is included herewith as Exhibit A.

Rejections Under 35 U.S.C. § 101

The Examiner rejects claims 1-6, 8-13, and 18 under 35 U.S.C. § 101, because, in the Examiner's view, the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. *See,* Paper No. 8, page 4. Applicants respectfully traverse this rejection as it may be applied to the newly presented claims.

The Examiner contends that "there is no description of the chemical, physical, or biological properties for the protein other than the sequence. The disclosed utilities associated with the claimed protein are based upon its homology with CTGF-1." *Id.* at page 5, lines 1-5. Applicants respectfully disagree with the Examiner's assertion that Applicants have not disclosed any properties for the protein other than the sequence. Applicants direct the Examiner's attention to the present specification, at, *e.g.*, pages 62-63 where CTGF-3 expression data is presented. Further, page 6, lines 10-21 in conjunction with Figures 2 and

3, present comparative analysis with CTGF-1 (Figure 2), as well as an analysis of the CTGF-3 structure in terms of antigenic regions, alpha, beta, turn, and coil regions, amphipathic regions, flexible regions, and hydrophilicity and hydrophobicity regions (Figure 3). Clearly, Applicants have characterized CTGF-3 beyond its nucleotide and amino acid sequence.

Regarding the issue of homology with CTGF-1, the Examiner states that Henikoff *et al. (Science 278*:609-614 (1997); of record) "teaches that shared modules in proteins are to be used as guides for further research. Furthermore, Henikoff expresses uncertainty about gene classification and family relationships are complex; computer-based tools may not be the solution." Paper No. 8, page 5, lines 7-11 (citations omitted).

With respect to the issue of using amino acid homology as a predictor of protein function, Applicants respectfully disagree with the Examiner's interpretation of Henikoff *et al.* The passages cited by the Examiner relate to the potential difficulties in creating taxonomical classifications of gene family members but do not refute the contention that members within a given gene family (based on amino acid sequence homology) tend to have homologous functions.

For instance, in the portion of Henikoff *et al.* the Examiner cites for the proposition that "family relationships are complex," *id.*, paragraph bridging pages 613-614, the authors of Henikoff *et al.* additionally state:

> Gene taxonomists have learned by now to cope with complexity in family relationships ... In fact, the task of classification is made easier for gene taxonomists than for Linnean [classical] taxonomists because sequence similarity is a precisely defined metric for establishing relatedness. This metric makes possible automated and computer-assisted classifications of genes.

Thus, although gene family relationships, according to Henikoff *et al.*, are complex, this complexity has been tempered by the extensive use of sequence similarity comparisons and computer assistance.

The Examiner also states, "the instant specification fails to correlate a specific function of CTGF-3 with any given module of CTGF-3, or even with the entire protein" and that "additionally, there is no art of record that discloses or suggests any activity for the claimed protein. Therefore, there is no well-established utility." Paper No. 8, page 5, lines 11-15. The Examiner concludes that "further experimentation is necessary to attribute a utility to the claimed protein" (Paper No. 8, page 6, line 8) and that "utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities." (Paper No. 8, page 6, lines 14-15). Applicants respectfully disagree.

As discussed in detail below, Applicants have in fact asserted specific and substantial utilities for the CTGF-3 protein. The Examiner states, however, that the utilities asserted in the specification are merely employed as the object of further research (which is non-patentable), and that the specification lacks evidence supporting these utilities. *Id.*, page 6, line 19, to page 7, line 2.

Legal Standard for Utility

The U.S.P.T.O. Utility Guidelines require that a claimed invention must possess either a well-established utility or an asserted utility that is specific, substantial and credible. *See,* M.P.E.P. § 2107.02 (Eighth edition, August 2001). If the claimed invention has a well-established utility that is specific, substantial and credible, utility exists for the invention and

a utility rejection is improper. *See* M.P.E.P. § 2107 (II) at 2100-29 (Eighth edition, August 2001). If, however, Applicants have asserted a utility for the claimed invention in the specification, the Examiner should determine whether any asserted utility is specific and substantial, and if so, whether such utility is credible to a person of ordinary skill in the art. *Id.*

Applicants further point out that they "need only make *one* credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112; additional statements of utility, even if not 'credible,' do not render the claimed invention lacking in utility." M.P.E.P. § 2107.02 (I.) at 2100-37 (Eighth edition, August 2001) (emphasis added); *see also In re Gottlieb*, 140 U.S.P.Q. 665, 668 (CCPA 1964) ("Having found that the antibiotic is useful for some purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes 'indicated' in the specification as possibly useful."). In fact, the Federal Circuit has indicated that

> [t]o meet the utility requirement, the Supreme Court has held that a new product or process must be shown to be "operable" - that is, it must be "capable of being used to effect the object proposed." Our cases have not, however, interpreted this language . . . to mean that a patented device must accomplish *all* objectives stated in the specification. On the contrary, "[w]hen a properly claimed invention meets at least one stated objective, utility under § 101 is clearly shown."

Carl Zeiss Stiftung v. Renishaw PLC, 20 U.S.P.Q.2d 1094, 1100 (Fed. Cir. 1991) (citations omitted) (quoting *Raytheon Co. v. Roper Corp.*, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984)).

Finally, the Examiner has the initial burden of challenging an Applicant's presumptively correct assertion of utility in the disclosure. *See, In re Brana*, 51 F.3d 1560,

1566 (Fed. Cir. 1995). To meet that burden, the Examiner must provide evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. *See, id.* Only after the Examiner has provided such evidence does the burden shift to the Applicant to provide rebuttal evidence "sufficient to convince [a person skilled in the art] of the invention's asserted utility." *Id.*

Applicants respectfully submit that the Examiner has not met his initial burden of demonstrating that a person of ordinary skill in the art would reasonably doubt Applicants' assertions of utility for the currently claimed invention.

Applicants' Assertions of Utility

The present specification fully and clearly sets forth utility for the claimed invention. For example, Applicants have asserted that the claimed invention is useful in the diagnosis and prognosis of various connective tissue related disorders where there is significantly altered expression of CTGF-3. *See,* Specification, page 30, lines 21-26. Within the specification, non-limiting examples of diseases or conditions caused by, associated with, or characterized by an over- or under- growth of connective tissue cells are set forth, including cancer, arthritis, fibrosis, atherosclerosis, and osteoporosis. *See,* Specification, page 30, line 26, to page 31, line 2. Indeed, the present specification teaches that increased levels of CTGF-3 can be detected in body fluids or tissues from mammals with cancer, fibrosis, arthritis, or atherosclerosis. In particular, the specification states:

> Thus, the invention provides a diagnostic method useful during diagnosis of connective-tissue related disorders, such as cancer, fibrosis, arthritis, or artherosclerosis, which involves assaying the expression level of the gene encoding the connective tissue growth factor-3 protein in mammalian

> cells or body fluid and comparing the gene expression level with a standard connective tissue growth factor-3 gene expression level, whereby an increase in the gene expression level over the standard is indicative of these diseases.

Specification, page 31, lines 7-13.

The utility of the claimed invention for the detection of cancer in particular is also asserted in the specification at page 32, lines 25-29: "The present invention is useful for detecting cancer in mammals. In particular, the invention is useful during diagnosis of the following types of cancers in mammals: breast, ovarian, cervical, prostate, bone, liver, lung, pancreatic, and splenic."

The specification further discloses that where a connective tissue related disorder has already been diagnosed according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced CTGF-3 gene expression will experience a worse clinical outcome relative to patients expressing the gene at a lower level. *See,* Specification, page 31, lines 14-18.

In addition, therapeutic uses for the CTGF-3 protein, as well as antibodies to the CTGF-3 protein, are asserted in the specification, including the treatment of individuals who are in need of an increased or decreased level of CTGF-3. *See,* Specification, pages 41-47.

It is evident that Applicants have specifically asserted utilities for the claimed invention relating to the detection and treatment of a variety of connective-tissue related disorders associated with an excess or deficiency of CTGF-3 activity. Cancer is a CTGF-3-related disorder that is explicitly named (Specification, page 30, line 26, to page 31, line 1).

Indeed, as will be discussed below, experimental results by other groups support the asserted role of CTGF-3 in cancer diagnosis and therapy.

Documents Supporting Applicants' Asserted Utilities

Applicants direct the Examiner's attention to and request consideration of the following documents which provide experimental support for Applicants' originally asserted utility of CTGF-3 in the diagnosis, prognosis, and/or treatment of cancer (although, as will be discussed, they utilized nomenclature different than "CTGF-3"): WO 98/58063 ("AN1"), WO 99/14327 ("AO1"), WO 99/21998 ("AP1")[2], Pennica *et al., Proc. Natl. Acad. Sci. USA 95*: 14717-14722 (1998)(AR7), all of record from the IDS filed August 15, 2001, as well as Saxena *et al., Mol. Cell. Biochem. 228*:99-104 (2001)(copy submitted with 3rd Supplemental IDS; AR15); Zoubine *et al., Biochem. Biophys. Res. Comm. 282*: 421-425 (2001)(copy submitted with 3rd Supplemental IDS; AS15); Inadera *et al., Biochem. Biophys. Res. Comm. 275*: 108-114 (2000)(copy submitted with 3rd Supplemental IDS; AS14); and Inadera *et al., Biochem. Biophys. Res. Comm. 294*: 602-608 (2002)(copy submitted with 3rd Supplemental IDS; AT14).

A nucleotide sequence and corresponding protein identical to CTGF-3, designated GRFLP, is disclosed in AN1. In AN1, it states: "GRFLP is expressed in various libraries derived from cancerous tissues. Therefore, GRFLP appears to play a role in cancer and

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[2]It is noted that the U.S. patent corresponding to WO 99/21998 ("AP1")-- U.S. Patent 6,387,657--has issued on May 14, 2002; a copy of the '657 U.S. Patent is enclosed in the 3rd Supplemental IDS filed concurrently herewith (AB1). It is also noted that the claims in the '657 patent are directed to WISP-1, not WISP-2.

connective tissue disorders, particularly disorders in which GRFLP is overexpressed." AN1, page 22, lines 28-30.

A nucleotide sequence and corresponding protein identical to CTGF-3, designated PRO261, is disclosed in AO1. In AO1, it was demonstrated that the gene encoding PRO261 was amplified in (1) primary lung tumors, (2) primary colon tumors, (3) colon tumor cell lines, and (4) breast tumor cell lines, relative to normal tissues. AO1, page 70, lines 16-34.

In both AP1 and Pennica *et al.*, the nucleotide sequence and corresponding protein identical to CTGF-3, is designated WISP-2. The following results are presented, supporting a utility for CTGF-3 in the diagnosis, prognosis, and treatment of cancer. First, these two documents demonstrate that the gene encoding WISP-2 is localized to a region on chromosome 20q12 that is a frequent site of DNA amplification in human breast and colon cancers. *See,* AP1, page 58, lines 25-28, and Pennica *et al.*, page 14720, column 2, paragraph 1. Second, as in AO1, it is demonstrated in AP1 that the gene encoding WISP-2 was amplified in (1) primary lung tumors, (2) primary colon tumors, (3) colon tumor cell lines, and (4) breast tumor cell lines, relative to normal tissues. *See*, AP1, page 87, line 27, to page 88, line 3. Third, in AP1, it is shown through *in situ* hybridization that there is particularly strong WISP-2 expression in benign fibroblast-like cells adjacent to infiltrating breast carcinoma cells. *See id.*, page 93, lines 3-17. Finally, in Pennica *et al.*, it is shown through quantitative PCR that the copy number of the gene encoding WISP-2 was increased 2-4 fold in 92% of human colon tumors studied. *See,* Pennica *et al.*, at page 14720, right column, 3rd full paragraph. Interestingly, however, despite DNA amplification of WISP-2, mRNA expression was reduced in the majority of colon tumors. *Id.*, page 14722, left column, first full paragraph. Pennica *et al.* concludes that "[t]he amplification and altered

expression patterns of the WISPs in human colon tumors may indicate an important role for these genes in tumor development." *Id.*, last paragraph.

Saxena *et al.*, using differential display, RT-PCR, and DNA sequencing analyses in normal human mammary epithelial cells (HMEC) and various breast tumor cell lines including MCF-7, ZR-75, T-47D and SKBR2, demonstrated that WISP-2 genes (corresponding to "CTGF-3") are differentially transcribed in normal and breast tumor cells. WISP-2 mRNA transcription was significantly higher in all 4 tumor derived cell lines, but mRNA expression was undetected or minimally detected in normal breast epithelial cells. Saxena *et al.*, page 103, right column. The Saxena Abstract concludes: "The mRNA expression profiles of WISP genes in normal breast epithelial cells and breast tumor derived cell lines indicated a strong possibility of the involvement of WISP-signaling in the development of human breast tumors, and can be utilized as genetic markers of this disease."

Zoubine *et al.* demonstrates that WISP-2 expression was undetectable, or minimally detectable, in normal human mammary epithelial cells, but was overexpressed in MCF-7 breast cancer cells. Expression of WISP-2 in MCF-7 cells was modulated by serum and correlated with the serum-induced MCF-7 tumor cell proliferation, suggesting that WISP-2 is serum responsive and may be a positive regulator of tumor cell proliferation. *See*, Zoubine *et al.*, Abstract, and page 425, last paragraph.

Inadera *et al.* (2000) presents results on WISP-2 in connection with their search for novel estrogen-responsive genes. Serial analysis of gene expression (SAGE) for estrogen-treated MCF-7 human breast cancer cells was performed. SAGE analysis of 31,000 and 30,856 tags from non-treated and 17 beta-estradiol (E2)-treated cells for 24 hours, respectively, facilitated the identification of 15,037 different transcripts. Comparison of

these two SAGE libraries indicated a remarkable similarity in expression profiles. Among the identified transcripts, four genes were found to be markedly increased for E2-treated cells compared with control cells. Three of the transcripts were known estrogen-inducible genes. The fourth gene was WISP-2, which the authors state has recently been reported as an up-regulated gene in the mammary epithelial cell line C57 MG transformed by the Wnt-1 oncogene. *See*, Inadera *et al.* (2000) Abstract. The increase in WISP-2 mRNA was completely prevented by co-incubation with a pure anti-estrogen ICI 182,780, but not by coincubation with cycloheximide, indicating that WISP-2 is directly regulated by the estrogen receptor. The WISP-2 gene was also induced by treating with environmental estrogens. This study represents the first comprehensive gene expression analysis of estrogen-treated human breast cancer cells. Thus, WISP-2 was identified as a novel estrogen responsive gene in human breast cancer cells and this effect is directly regulated by an estrogen receptor. *Id.*, page 114, last paragraph.

In a subsequent paper, Inadera *et al.* (2002) examined whether WISP-2 could be utilized as a marker for screening environmentally relevant compounds for estrogenicity. In MCF-7 cells, progesterone, dexamethasone, tri-iodothyronine, and 2,3,7,8-tetrachlorodibenzo-p-dioxin did not regulate the expression of WISP-2, indicating that its induction is highly specific for hormones that interact with the estrogen receptor. Western blot analysis detected WISP-2 protein induced by 17-beta-estradiol (E2), not only in the cell lysates but also in the culture supernatant of exposed cells, indicating that WISP-2 was a secreted protein. The induction of WISP-2 protein by E2 in the culture supernatant was dose-dependent with estimated EC(50) levels between 10 and 100 pM. These results

demonstrated the capacity to screen environmental compounds for estrogenicity via WISP-2 induction.

Clearly, the numerous publications discussed above support and substantiate Applicants' assertion of CTGF-3's utility in the diagnosis, prognosis, and/or treatment of cancer, and in particular, human breast cancer.

Compliance with the Utility Guidelines

Regarding the specificity of an asserted use, Applicants note that the Utility Guidelines define "specific utility" as a utility that

> is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. . . . A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

M.P.E.P. § 2107.01 (I.) at 2100-32 (Eighth edition, August 2001).

Applicants assert that the specification does not provide "[a] general statement of diagnostic utility, such as diagnosing an unspecified disease." Rather, in view of Applicants' assertions in the specification that CTGF-3 is useful in the diagnoses of cancer, coupled with the fact that the CTGF-3 gene was consistently found to be overexpressed in human breast cancer cells (thus confirming and supporting Applicants' assertions), Applicants submit that the claimed invention possesses diagnostic and/or prognostic utility in a specified disease state, *i.e.*, cancer, such as breast cancer. Accordingly, since there is "a disclosure of what condition can be diagnosed," it follows that the statement of diagnostic/prognostic utility is clearly sufficient under the Utility Guidelines.

Applicants also note that the Utility Guidelines define "substantial utility" as a utility that

> defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities . . . An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring.

M.P.E.P. § 2107.01 (I.) at 2100-32 (Eighth edition, August 2001).

As noted above, Applicants have asserted that CTGF-3 can be overexpressed in cancer (Specification, page 31, lines 3-13), and have disclosed assays which measure the presence of CTGF-3 in a biological sample (Specification, page 32, line 1, to page 36, line 16). Thus, not only would such assays have utility in diagnosing cancer, but also in further monitoring clinical outcome, *i.e.*, in prognosis. Clearly, these are substantial "real world" utilities. Thus, similar to the "specific" prong, Applicants' asserted utility therefore clearly satisfies the "substantial" prong of the Utility Guidelines.

Regarding the credibility of an asserted utility, the Utility Guidelines provide as follows:

> Where an applicant has specifically asserted that an invention has particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong," even when there may be reason to believe that the assertion is not entirely accurate. Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided).

M.P.E.P. § 2107.02 (III.)(B.) at 2100-40 (Eighth edition, August 2001). In other words, the Examiner "must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art." M.P.E.P. § 2107.02 (III.)(A.) at 2100-40 (Eighth edition, August 2001). Applicants respectfully submit that the Examiner has not met this burden.

Applicants re-emphasize that they need only make *one* credible assertion of specific utility for the claimed invention to satisfy the utility requirements, and that once the claimed invention has been found to be useful for some purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes indicated in the specification as possibly useful. *See, Carl Zeiss Stiftung v. Renishaw plc*, 20 U.S.P.Q.2d 1094, 1100 (Fed. Cir. 1991); *In re Gottlieb*, 140 U.S.P.Q. 665, 668 (CCPA 1964); M.P.E.P. § 2107.02 (I.) at 2100-37 (Eighth edition, August 2001).

Applicants have asserted in the specification that the claimed invention can be used in the diagnosis, prognosis, or treatment of cancer, and have provided "evidence" in the form of art to substantiate these assertions and provide evidence as to the accuracy, *i.e.*, credibility, of these assertions. Thus, Applicants submit that the above assertions are not only specific and substantial, but credible as well, *i.e.*, the assertion is *at least believable* to, and would not be considered *false* by, a person of ordinary skill in the art. The Examiner has not provided any evidence showing that one of ordinary skill in the art would reasonably doubt these asserted utilities. Thus, a *prima facie* case of lack of utility has not been established.

Conclusion: The Utility Requirement Has Been Satisfied

In view of the above, Applicants assert that the utilities assigned to the claimed invention are specific, substantial and credible. Even assuming, *arguendo*, the Examiner had established a *prima facie* showing that the claimed invention lacks utility, Applicants respectfully submit that the numerous publications cited herewith (*i.e.*, the evidence of record) would be sufficient to lead one skilled in the art to conclude that the asserted utility would not be considered "false" by a person of ordinary skill in the art, and therefore sufficient to rebut the Examiner's showing. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 101.

Rejection Under 35 U.S.C. § 112, First Paragraph

How to Use Requirement

At page 7 of Paper No. 8, the Examiner rejects claims 1-13 and 18 under 35 U.S.C. § 112, first paragraph. In the Examiner's opinion, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility... "one skilled in the art clearly would not know how to use the claimed invention." Paper No. 8, page 7, lines 7-10. Applicants respectfully traverse this rejection.

For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, as well as the art cited therein, Applicants assert that the claimed invention complies with the current case law and is supported by a specific, substantial and credible utility as well. The Examiner "should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. 101 rejection is proper." M.P.E.P. § 2107.01 (IV.)

at 2100-36 (Eighth edition, August 2001). Therefore, since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility of the claimed invention, should be withdrawn.

Biological Deposit

At pages 7-8 of Paper No. 8, the Examiner rejects claims 1-6, 9-13, and 18 under 35 U.S.C. § 112, first paragraph, for non-enablement because the specification allegedly lacks complete deposit information for the deposit of ATCC Deposit No. 97756. The Examiner contends that Applicants' reference to the deposit of ATCC Deposit No. 97756 in the specification (the paragraph bridging pages 3-4 is cited) is insufficient to ensure that all of the conditions of 37 C.F.R. § 1.801-1.809 have been met.

A Statement Concerning the ATCC Deposit, signed by an attorney of record, is submitted concurrently herewith.

Applicants respectfully submit that since the deposit was made before the earliest filing date of the present application, a chain of custody declaration is not necessary. Also, concerning the correct address for the ATCC, Applicants direct the Examiner to page 7, lines 1-5, of the specification where the new address of the ATCC depository is already recited.

In view of the above remarks, withdrawal of this rejection is respectfully requested.

Written Description

At pages 9-11 of Paper No. 8, the Examiner rejects claims 1, 5, 6, 8-10, and 13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner contends that Applicants have not provided adequate written description of the claimed genus of polynucleotides since the specification does not provide sufficient recitation of distinguishing identifying characteristics of the genus. The factors to be considered, according to the Examiner, include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The Examiner states that the only factor present in the present claim is a partial or variable structure. Accordingly, the Examiner concludes that only polynucleotides comprising the nucleotide sequence of SEQ ID NO:1, but not the full breadth of the claim, meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse this rejection.

Solely to advance prosecution and not in acquiescence to the Examiner's rejection, the claims under rejection have been canceled. It is believed that this rejection is inapplicable to the new claims. Applicants submit that this rejection has been overcome and should be withdrawn.

Enablement

At pages 11-14 of Paper No. 8, the Examiner rejects claims 1, 5, 6, 8-10, and 13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner states that the claims are broad because "they do not require the claimed polynucleotide to be identical to the disclosed sequence and because the claims have no functional limitation. The specification does not teach the skilled artisan how to use the claimed polynucleotides encoding CTGF-3 for purposes unrelated to or divorced from a biological activity. Therefore, the skilled artisan is not provided with sufficient guidance to use the claimed polynucleotides. Paper No. 8, page 12, lines 16-22. Further, the Examiner states:

> For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of the claimed polynucleotides and lack of knowledge about function(s) of encompassed polynucleotides and polypeptides structurally related to CTGF-3, the lack of direction or guidance for using polynucleotides and polypeptides that are not identical to CTGF-3, and the breadth of the claim encompassing structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

Paper No. 8, page 14, lines 3-9. Applicants respectfully traverse this rejection.

At the outset, Applicants note that aspects of this rejection appear redundant to the § 112, first paragraph, "how to use" rejection, which preceded the utility rejection under 35 U.S.C. § 101. If that is the case, and the rejection is maintained, the Applicants respectfully request that the issues be consolidated.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, the claims under rejection have been canceled. It is believed that this rejection will not be found applicable to the new claims. Applicants submit that this rejection has been overcome and should be withdrawn.

The Examiner also states that claim 8 is non-enabled because it is unclear if the antecedent basis for the term "or a subfragment thereof" is the claimed polynucleotide or SEQ ID NO:11. According to the Examiner, since a single nucleotide is a subfragment,in the case where the antecedent is SEQ ID NO:11, the present specification has not enabled a polynucleotide that does not contain a single nucleotide of SEQ ID NO:11. Applicants respectfully traverse this rejection.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, claim 8 has been deleted in favor of new claim 48, which does not contain the objectionable language. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

At pages 15-16 of Paper No. 8, the Examiner rejected the claims under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite, on several grounds. Each ground of rejection will be addressed in turn.

At page 15, lines 4-8, of Paper No. 8, the Examiner states that claims 3, 4, and 13 are indefinite because they recite the term "connective tissue growth factor-3." According to the Examiner, because the specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "connective tissue

growth factor-3," an artisan cannot determine what additional or material structural or functional limitations are placed upon a claim by the presence of this element.

Similarly, at page 15, lines 10-14, of Paper No. 8, the Examiner states that claims 1, 3-6, 9-13, and 18 are indefinite because they recite the term "connective tissue growth factor-3." The reasons stated above are cited for this rejection as well. Although Applicants were preparing to address the second rejection, since it included the larger number of claims, Applicants cannot locate the language "connective tissue growth factor-3" in several of the claims (*e.g.*, claims 5 and 9-12).

The above notwithstanding, Applicants respectfully request that the Examiner reconsider and withdraw this rejection in view of the new claims, which do not contain the objectionable language.

At page 15, lines 16-20, of Paper No. 8, the Examiner rejects claims 1, 4-6, 9-13 and 18[3] under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting the term "mature." Applicants disagree with this rejection as one skilled in the art of molecular biology and genome sequencing would clearly understand what is meant by the term "mature" protein. Further, the term is defined clearly in the specification, at page 8, line 12, to page 9, line 28. It is respectfully requested that this ground of rejection be reconsidered and withdrawn.

At page 16, lines 1-6, of Paper No. 8, the Examiner rejects claim 5 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting the term "stringent hybridization conditions" because stringency varies according to the hybridization

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[3]Applicants assume the Examiner rejected the dependent claims.

conditions and the particular hybrid under study. The Examiner contends that the specification fails to precisely define "stringent conditions" and that any degree of stringency is embraced by the claims. Applicants respectfully traverse this rejection.

Contrary to the Examiner's assertion, page 12, lines 23-27, of the specification specifically defines the term "stringent hybridization conditions." It is well known that the claims are not read in a vacuum; they are read in light of the specification, and are read in view of the knowledge of one skilled in the art. Applicants respectfully submit that one skilled in the art would be apprised of the metes and bounds of claim 5 without ambiguity or misunderstanding. The above notwithstanding, Applicants submit that claim 5 has been canceled rendering this rejection moot. The new claims do not recite the objectionable language. Accordingly, this ground of rejection should be reconsidered and withdrawn.

At page 16, lines 8-14, of Paper No. 8, the Examiner rejects claim 8 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting the term "or a subfragment thereof." The Examiner contends that it is not clear if the fragment comprises at least 50 contiguous nucleotide of nucleotide 1-231 of SEQ ID NO:1, or if the fragment is at least 50 nucleotides long irrespective of nucleotide composition.

Claim 8 has been canceled in favor of new claim 48 for clarity. Applicants believe that the metes and bounds of new claim 48 are clear. Accordingly, this ground for rejection can be withdrawn.

Claim Objections Regarding Improper Dependent form

At pages 16-17 of Paper No. 8, the Examiner objects to claims 5 and 6 under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Specifically, the Examiner states that a polynucleotide that hybridizes to (a)-(f) of claim 1 fails to further limit the isolated nucleic acid molecule of claim 1 and that a polynucleotide encoding an epitope bearing portion of (a)-(f) of claim 1 fails to further limit the isolated nucleic acid molecule of claim 1. The Examiner also states that dependent claims shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim, but dependent claims 5 and 6 include only a portion of the limitations of the claim incorporated by reference into the dependent claims.

Applicants have canceled claims 5 and 6, rendering this rejection moot. Withdrawal thereof is respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

At page 17 of Paper No. 8, the Examiner rejects claim 8 under 35 U.S.C. § 102(b) as being anticipated by Purchio (EP Application 0 495 674 A2). It appears that this rejection has been made due to the alleged unclear antecedent basis for the term "subfragment thereof" in claim 8, as well as the Examiner's statement that "a single nucleotide is a subfragment." According to the Examiner's interpretation of claim 8, whereby the 'claimed polynucleotide' is the antecedent for "subfragment thereof" (*See*, Paper No. 8,

page 17, lines 15-21), the Examiner contends that Purchio meets the limitations of claim 8.

As claim 8 has been canceled, this rejection is rendered moot. Withdrawal of this rejection is respectfully requested.

At pages 17-18 of Paper No. 8, the Examiner rejects claim 6 under 35 U.S.C. § 102(b) as being anticipated by Grotendorst *et al.* (U.S. Patent 5,408,040) in view of Benjamini (Immunology: A Short Course, Leskowitz (ed.) Wiley-Liss, Inc., New York, N.Y., July 1991, page 40). According to the Examiner:

> Grotendorst teaches an isolated nucleic acid molecule encoding the amino acid sequence "dvrlps" (Example 4) which is identical to the amino acid sequence of residues 137-142 of the present application's SEQ ID NO:2. Various studies indicate that the size of an epitope is approximately equivalent to 5-7 amino acids. See, Benjamini, page 40. Claim 6 fails to further limit the subject matter of claim 1. Accordingly, Grotendorst teaches an isolated nucleic acid molecule comprising a polynucleotide which encodes the amino acid sequence of an epitope-bearing portion of a CTGF-3 polypeptide having an amino acid sequence in (a), (b), (c), (d), (e), or (f) of claim 1.

Paper No. 8, page 17, lines 23-24, to page 18, line 7.

As claim 6 has been canceled, this rejection is rendered moot. Withdrawal of this rejection is respectfully requested.

At page 18 of Paper No. 8, the Examiner rejects claim 5 under 35 U.S.C. § 102(b) as being anticipated by Perbal (WO 93/00430 A1). According to the Examiner:

> Claim 5 fails to further limit the subject matter of claim 1. The metes and bounds of "stringent hybridization conditions" are not clearly set forth. Nucleotides 9-758 of the present application's SEQ ID NO:1 encode the amino acid sequence of the present application's SEQ ID NO:2. Perbal discloses an isolated nucleic acid molecule that is 56% identical to nucleotide 9-758 of the present application's SEQ ID NO: 1

> (page 26) (DNA alignment omitted). The nucleic acid molecule or its complenent would hybridize under stringent hybridization conditions to a polynucleotide having a nucleotide sequence identical to a nucleotide sequence in (a), (b), (c), (d), (e), or (f) of claim 1.

Paper No. 8, page 18, line 9, to page 19, line 28.

As claim 5 has been canceled, this rejection is rendered moot. Withdrawal of this rejection is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the Specification

Please replace the paragraph beginning on page 6, line 10, and ending on line 12, with the following paragraph:

> **Figure 2** shows the regions of similarity between the amino acid sequences of the connective tissue growth factor-3 protein (SEQ ID NO:2) and connective tissue growth factor-1 (SEQ ID NO:3).

Please replace the paragraph beginning on page 8, line 6, and ending on line 11, with the following paragraph:

> The determined nucleotide sequence of the connective tissue growth factor-3 cDNA of SEQ ID NO:1 contains an open reading frame encoding a protein of 250 amino acid residues, a predicted leader sequence of about 19 amino acid residues, and a deduced molecular weight of about 26 kDa. The connective tissue growth factor-3 protein shown in SEQ ID NO:2 is about 44% identical and about 59% similar to human connective tissue growth factor-1 (SEQ ID NO:3)(Figure 2).

In the Claims

Claims 1-6 and 8-23 have been canceled.

Claims 24-67 have been added.